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OCTOBER 3, 1988

CHEMICAL & ENGINEERING

NEWS

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HEART DRUGS

Annual sales head toward $10 billion

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CHEMICAL & ENGINEERING
NEWS
Volume 66, Number 40
CENEAR 66 (40) 1–104
ISSN 0009-2347
OCTOBER 3, 1988

News of the Week

■ **Theorists conclude that room-temperature superconductivity probably cannot be achieved in copper oxides.** **Page 6**

■ **James D. Watson is appointed head of NIH's human genome research program.** **Page 7**

■ **NAE president criticizes failure to establish an effective U.S. technology policy.** **Page 7**

■ **EPA recommends a complete phaseout of chlorofluorocarbon and halon production.** **Page 8**

■ **Chemical contamination of air, water, and food found to be worse in developing countries.** **Page 8**

■ **Photos from the ACS national meeting in Los Angeles.** **Page 9**

■ **ACS meeting is attended by over 12,000 conferees.** **Page 9**

■ **Congressman chides chemists for their low level of activism in the political arena.** **Page 10**

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Business

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Government

Latest bill attempting to revise pesticide law was passed by the House, largely because the most controversial parts were dropped. **Page 19**

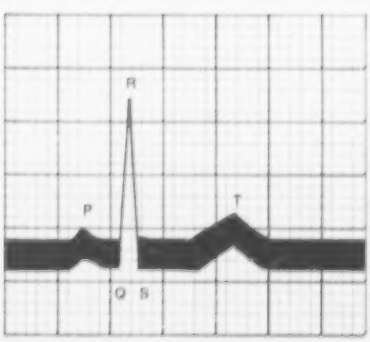
Technology

Argonne National Laboratory's coal sample program is supplying well-characterized samples of eight U.S. coal types to qualified coal researchers. **Page 29**

New type of solar cell shows promise for generating electricity and for process-scale electrolysis. **Page 32**

Books

"Effective Writing Strategies for Engineers and Scientists" and "The Basics of Technical Communicating" offer scientists instruction, encouragement, and rules of correct English. **Page 71**



Product Report

Market for cardiovascular drugs will grow 16% per year to $9.6 billion in 1992 as drug industry steps up efforts to advance therapy for disease that remains the leading cause of death in the U.S. **Page 35**

Chemical & Engineering News

1155—16th St., N.W., Washington, D.C. 20036

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Published by
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(202) 872-4600; TDD (202) 872-8733
John K Crum, Executive Director

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Subscription Rates 1988. Printed editions: nonmembers U.S. 1 yr. $49, 2 yr. $83, outside U.S. 1 yr. $75, 2 yr. $135. Air freight rates available on request. Rates above do not apply to nonmember subscribers in Japan, who must enter subscription orders with Maruzen Co. Ltd., 3-10 Nihonbashi 2-chome, Chuo-ku, Tokyo 103, Japan. Tel: (03) 272-7211. Single copies: Current $7.00. Rates for back issues and volumes are available from Microforms & Back Issues Office, ACS, 1155—16th St., N.W., Washington, D.C. 20036. Back and current issues available on microfilm and microfiche. Rates on request from Microform Program, ACS.

Chemical & Engineering News (ISSN 0009-2347) is published weekly except for the last week in December by the American Chemical Society at 1155—16th St., N.W., Washington, D.C. 20036. Second-class postage paid at Washington, D.C., and additional mailing offices. POSTMASTER: Send address changes to Chemical & Engineering News, Membership & Subscription Services, P.O. Box 3337, Columbus, Ohio 43210. ACS assumes no responsibility for the statements and opinions advanced by the contributors to its publications.

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LETTERS

Disposal of plastics

SIR: Your article on polyethylene and an impending raw material crunch (C&EN, Aug. 29, page 12) reports a growing demand for plastics. From whom? I wonder. Surely, not the consumer.

I resist the purchase of food in plastic and search the grocery store shelves for glass bottles. I ask for paper bags rather than plastic. Recently, I abandoned plastic garbage bags in favor of new "leaf" paper bags, which hold a comparable amount of garbage.

Why are we, as a nation, so eager to put a nonrenewable resource like petroleum into plastic products—especially those associated with the food industry—that have a limited product life only to go to a landfill for centuries?

Manufacturers may say that plastics are cheaper than alternatives. However, plastics are only cheaper until their disposal costs are counted.

Further, what will happen to the American economy—so wedded to plastic packaging—when the next jump in oil prices occurs? Wouldn't it make more sense to save the use of plastic for those products that need long-term durability?

Suzanne D. LaLonde
Syracuse, N.Y.

Energy conservation

SIR: The letter from Rep. Claudine Schneider (C&EN, July 11, page 2) cannot go unanswered. Because of her position, Schneider is able to influence the course of our future to a much greater extent than most individuals. The exercise of this influence needs to be tempered by a clear view of the real world.

In the first place, the business community, which understands economics very well, has for decades steadily invested in energy conservation in response to movement in energy prices. It will continue to do so as prices rise further. We need both rational conservation and the assurance of a sufficiently affordable energy supply to give people the confidence to plan for future growth. Real growth in electricity demand is averaging almost 4% a year as our economy still continues to expand. To my knowledge, no responsible people actually in the business of providing energy can subscribe to the exaggerated claims for conservation that she cites.

Second, the safety record and pollution problems of fossil-based electricity have been widely documented. There is sound justification, for environmental and safety reasons alone, to begin a program of replacing our fossil plants with nuclear plants, even with no growth in demand.

Finally, as every beginning student of nuclear technology understands, power reactors do not produce weapons-grade plutonium. It is contaminated with too much ^{240}Pu to be useful, and cannot even be separated from the spent reactor fuel without sophisticated processing facilities. It is shameful that an elected official, with the privilege of office, neglects to exercise the responsibility of being factually accurate.

B. R. McElmurry
Rancho Palos Verdes, Calif.

Doctorate in chemical research

SIR: The discussion in C&EN about contributions of non-Ph.D.s and suggestions of a doctorate in chemical research (letters by Joseph Levine, May 30, page 3; A. J. Reid, April 18, page 3; Robert M. Kuhn, March 7, page 4; and Mario Altamura, Nov. 23, 1987, page 2) remind me of the medieval religious discussion about how many angels can dance on a tip of a needle.

Actually, the issue in question is extremely simple. First, the Ph.D. title is not a prerequisite for brilliant scientific achievement. Second, a person with such achievemen. does not need the doctor title to enhance his or her stature.

Thomas Alva Edison's formal education was limited to three years in public school, but his scientific achievements surpass those of most Ph.D.s. I do not think that he needed the title "doctor in research" to advance his career or enhance his fame.

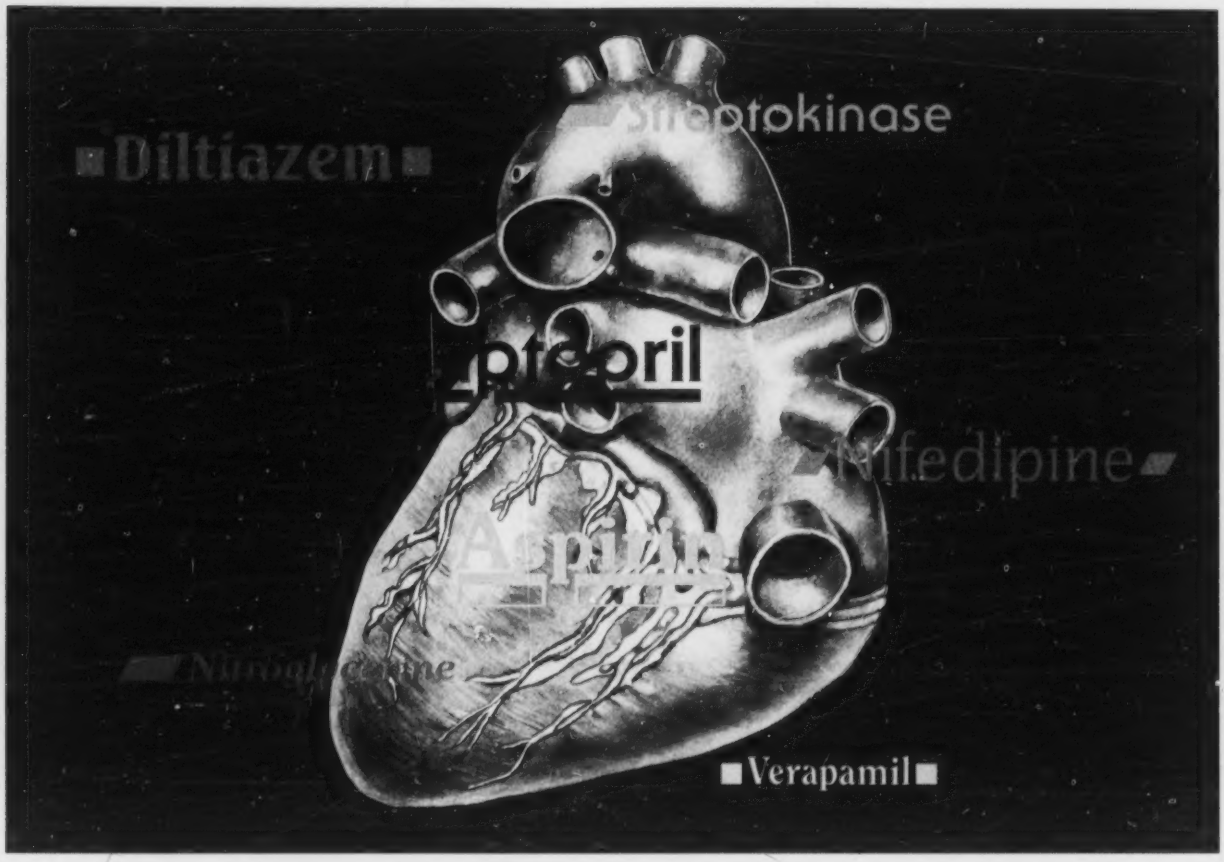
Jacob Rosin
Emeritus member
Netanya, Israel

Uses for silcones

SIR: It is with pleasure that I read Earl L. Warrick's book review of "Silicon and Silicones" (C&EN, Aug. 1, page 43).

It is not well known or publicized that both Dr. Sullivan, former director of research of Corning Glass, and Frederic Kipping had given up on silicones as giving anything practical. In fact, Kipping reports just a small amount of an oily substance as the description of the first silicones made.

In late 1938 or early 1939, Sullivan invited my father to Corning Glass to discuss silicones. At that time, Sullivan



Drug Industry Steps Up Fight Against Heart Disease

Stephen C. Stinson,
C&EN Northeast News Bureau

Despite advances in pharmacology and public awareness of risk factors, heart disease remains the leading cause of death in the U.S., accounting for 37% of the total. However, the death rate from heart disease has dropped dramatically over the past 20 years from 367 to 323 per 100,000 population. This progress has led to renewed efforts by medicinal chemists, molecular biologists, and physicians to advance therapy further.

The unparalleled potential for such advances in the near future and the sheer size of the market have caused the drug industry worldwide to devote a large share of its resources to the quest. Karl Habermas, analyst at the investment research and management firm of Sanford C. Bernstein & Co., estimates that the market for cardiovascular drugs will grow 16% per year to $9.6 billion in 1992 from $4.5 billion in 1987.

Of this 16% growth, Habermas expects approximately equal contributions to come from increased numbers of prescriptions written, price increases of established drugs, and "mix upgrade." Mix upgrade is a shift in doctors' prescribing from older to newer drugs, which are patent-protected and thus costlier.

Medical observers attribute progress against heart disease to date to reduction of risk factors for atherosclerosis, the most common cause. Risk factors include hypertension (high blood pressure), hypercholesterolemia (high concentrations of blood cholesterol), eating too much saturated fat, and smoking.

As it affects the heart, atherosclerosis is narrowing of coronary arteries, which supply heart muscle. Narrowing results from combined proliferation of smooth muscle cells through arterial inner walls, aggregation of blood platelets, and deposition of cholesterol.

When atherosclerosis reduces arterial diameters to about 20% of normal values, heart muscle may suffer chronic oxygen deprivation (ischemia). Or a blood clot may lodge at

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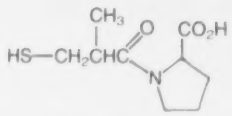
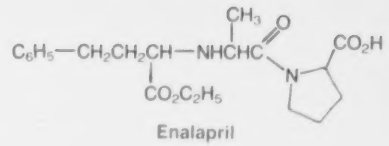
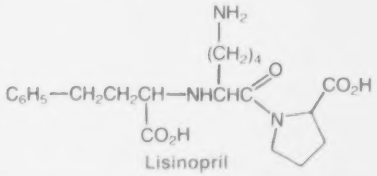
Treatment of hypertension and heart failure fuels growth for inhibitors of angiotensin converting enzyme



Captopril



Enalapril



Lisinopril

Enalapril is an inactive prodrug converted to the active agent enaprilat by hydrolysis of the ethyl ester in the liver

the site with acute oxygen deprivation and death of some heart muscle (heart attack).

Despite increased detection and treatment of hypertension, however, incidence of atherosclerotic heart disease in treated hypertensive patients remains high. And although drugs are available to lower blood cholesterol, unpleasant side effects have limited their widespread use. Survival rates of patients with heart failure have not improved despite availability of drugs effective against its symptoms. Heart failure is a progressive loss of contractile force from effects of hypertension, ischemia, and heart attacks.

About 60 million Americans have at least mild hypertension. The incidence in blacks is almost twice that in whites.

Doctors use various criteria to diagnose hypertension, but a common one is diastolic pressure, which is pressure between heartbeats. Normal blood pressure is considered to be 120 mm Hg systolic (at the heartbeat) and 80 mm Hg diastolic.

In this scheme, diastolic pressures of 90 to 104 are arbitrarily classed as mild hypertension, 105 to 114 as moderate, and over 115 as severe. Each 5-mm Hg increase in diastolic pressure raises incidence of heart attacks 20 to 25%.

The cause of nearly 90% of hypertension is unknown, which is why it is called essential hypertension. Whatever the cause, all of the mechanisms that control blood pressure interact with one another, each causing the other to drift toward abnormal states.

Increased sympathetic nervous activity increases heart rate and pumping capacity, constricts peripheral blood vessels, and stimulates renin and epinephrine secretion. Epinephrine is a neurotransmitter that adds its effect to that of norepinephrine at sympathetic receptors. Renin catalyzes conversion of the plasma protein angiotensinogen to angiotensin I, which is converted to angiotensin II by kinases.

Angiotensin II constricts blood vessels, stimulates release of aldosterone, and degrades bradykinin. Aldosterone reduces water and sodium excretion by kidneys. Bradykinin is a naturally occurring vasodilator. Sodium triggers release of more renin.

Also, buildup of sodium in smooth muscle cells renders them more sensitive to sympathetic nervous stim-

U.S. cardiovascular drug market pushes toward $10 billion

Class	Sales, $ millions 1987	1988	1992	Annual growth
β-Blockers	$1029	$1129	$1281	4%
Diuretics	653	651	563	−3
Antihypertension[a]	577	570	675	3
Calcium antagonists	738	1121	2834	31
Vasodilators[b]	543	573	676	4
ACE inhibitors	471	774	1997	33
Cholesterol lowering[b]	202	304	1054	39
Oral inotropes[b]	67	74	228	28
Other[b]	225	234	282	5
TOTAL	$4505	$5430	$9590	16%

a Drugs used only for hypertension, principally α-blockers. b Preliminary estimates. **Source:** Sanford C. Bernstein & Co.

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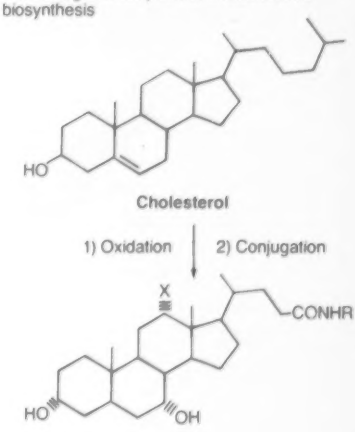
Bile acid sequestrants stimulate cholesterol consumption

Binding and excretion of bile acids prevent their reabsorption and reuse, thus stimulating consumption of cholesterol for biosynthesis



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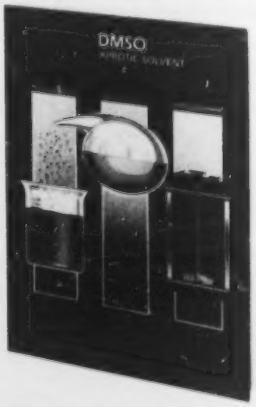

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ulation and leads to accumulation of calcium. Calcium changes cross-linking of actin and myosin molecules in cells, producing contraction. Untreated hypertension causes stiffening and narrowing of peripheral blood vessels, permanently raising resistance to blood flow.

Treatment of hypertension begins with loss of excess weight and restrictions on dietary sodium. Obesity increases the load on the heart. Excessive sodium causes the body to retain water. If these measures do not lower blood pressure sufficiently, doctors go on to drug treatment.

Earliest theories of the cause of hypertension included excess fluid volume in the circulatory system. This view led to the development of a stepwise drug regimen, which begins with prescribing a diuretic, typically a thiazide. Diuretics stimulate production of urine and excretion of sodium. They can also cause excess potassium excretion, however.

Potassium is important in nerve conduction and muscle contraction, and potassium depletion (hypokalemia) is dangerous to patients

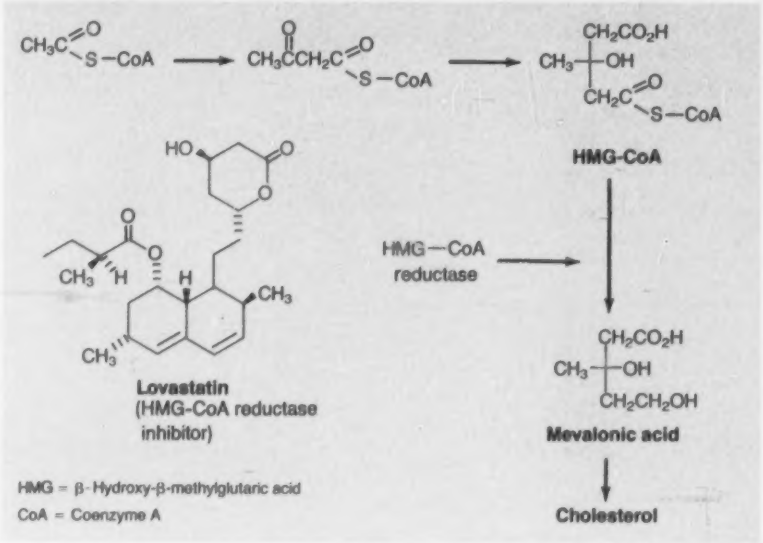
whose hearts are subject to arrhythmias (abnormal rhythms). Doctors correct hypokalemia by prescribing a potassium supplement or an additional, potassium-sparing diuretic like amiloride, spironolactone, or triamterene.

If blood pressure remains high with diuretics, doctors go on to the next step and prescribe an additional drug, usually a β-adrenergic blocking agent ("β-blocker"). Such β-blockers as propranolol are compounds whose molecular structures resemble those of the neurotransmitters epinephrine and norepinephrine in the sympathetic nervous system.

Those that block β_1-receptors in heart muscle slow heart rate and reduce contractile force. Those that block β_2-receptors in arteriolar smooth muscle dilate arterioles, thus reducing resistance in the circulatory system.

Some doctors prefer to use a β-blocker as step one and a diuretic as step two in young patients, those with angina (chest pain on exercising), and those who have had a heart attack. Black patients do not respond so well to β-blockers as do white patients, however, and β-blockers cannot be used with asthmatics. This is because blocking of β_2-receptors in bronchioles causes them to constrict.

Newer cholesterol-lowering agents inhibit biosynthesis



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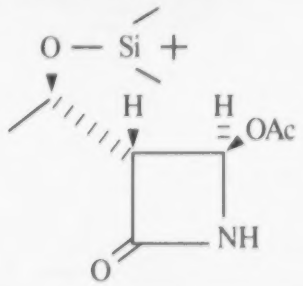

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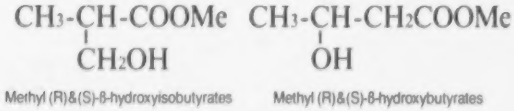
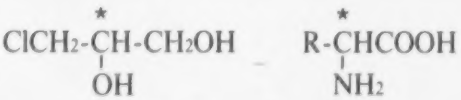


Methyl (R)&(S)-β-hydroxyisobutyrates

Methyl (R)&(S)-β-hydroxybutyrates



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If a third drug is needed, doctors usually add the vasodilator hydralazine. Hydralazine does not affect the sympathetic nervous system but decreases availability of calcium ions in smooth muscle cells. This reduces the contractile activity of arteriolar cell walls.

If a fourth drug is needed, doctors often add an α_2-agonist like clonidine or guanethidine to the others. Stimulation of α_2-receptors in the brain inhibits release of norepinephrine to heart and arteriolar smooth muscle receptors, thus also reducing heart rate and contractile force and dilating arterioles to reduce resistance to blood flow.

So in extreme cases, patients might take up to five drugs several times a day. Doctors worry that patients might not follow complicated medication schedules. And the cost of so many drugs might also daunt patients.

Pharmaceutical companies have responded by developing fixed combinations of drugs in a single tablet, new drugs or controlled-release forms of older drugs that are effective when taken once daily, and more potent drugs that lower blood pressure sufficiently when used alone (monotherapy). But to be useful, the fixed amounts must be identical to those that the doctor has found best for the individual patient. And it seems that every drug company can adduce clinical evidence that its newer products are effective as monotherapy.

Side effects can make treatment feel worse than hypertension, which has no symptoms until it causes heart failure, heart attack, stroke, kidney failure, or vision loss. Side effects of diuretics include impotence, and those of β-blockers include impotence and psychiatric depression. Occurrence of side effects can lead patients to stop taking medication.

Most discouraging have been studies that show that treated hypertensive patients still have a higher incidence of heart disease than the general population. One factor in this is that, although diuretics lower blood pressure, they raise serum concentrations of low-density lipoprotein (LDL) and lower those of high-density lipoprotein (HDL).

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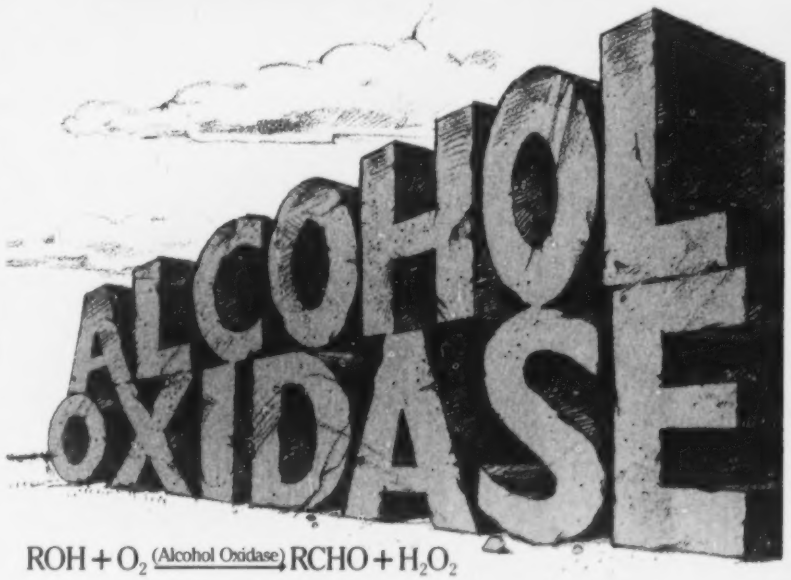

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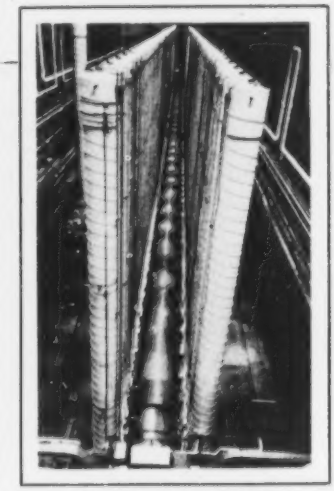

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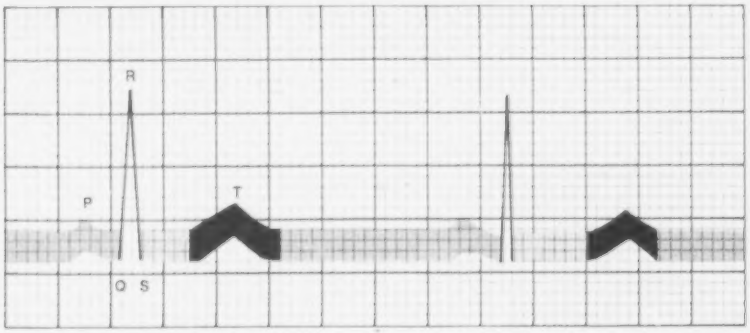
EKG patterns reveal electrical events in hearts



The electrocardiogram (EKG) gathers information about heart rate and rythym. It is not a mechanical record of heartbeats. Rather it records the electrical events that trigger contractions of atria, then of ventricles.

Heartbeat begins as the sinoatrial (SA) node, a clump of pacemaker tissue in the upper right atrium, depolarizes suddenly to +30 mV from −90 mV. Depolarization spreads in a domino effect throughout the atrium to the atrioventricular (AV) node at the bottom of the right atrium and is recorded as a P-wave. The AV node delays transmission of depolarization until the atria have contracted and driven blood into the ventricles.

The QRS complex starts with depolarization of the AV node. Depolarization travels down the wall between the right and left ventricles through the conductive bundle of His. The His bundle divides into right and left branches, which lead down to the bottom of the heart and up the sides of the ventricle to connect with the widely diffused, conductive Purkinje fibers in the ventricle walls. Conductive fibers in the ventricles repolarize, which is recorded as a T-wave.

Repolarization of the atria does not appear on the EKG because it is masked by the QRS complex. A U-wave sometimes appears after the T-wave and may represent repolarization of the Purkinje fibers.

LDL transports cholesterol in a way that enhances deposition on arterial walls. HDL also transports cholesterol, but high levels of HDL are associated with decreased risk for atherosclerosis.

The rationale for centering treatment around diuretics also has come into question, because excess fluid volume in the circulatory system seems important in only a few patients. Their effectiveness may come from lowering stresses of sympathetic nervous activity on blood pressure regulating systems.

Indeed, Habermas of Bernstein & Co. estimates that sales of diuretics will fall 3% per year to $563 million in 1992 from $653 million in 1987 as the number of prescriptions declines to 76.6 million from 97.7 million.

Doctors have come to focus on peripheral vascular resistance as the key element in hypertension. Increased understanding of blood pressure regulation has uncovered new targets for drugs. One target is angiotensin converting enzyme (ACE), which catalyzes conversion of angiotensin I to the vessel constrictor angiotensin II. Another is calcium, which stimulates smooth muscle contraction.

Captopril, developed by E. R. Squibb & Sons, and Merck & Co.'s enalapril and lisinopril are widely used ACE inhibitors. Such agents as nifedipine, marketed by Pfizer and Miles Laboratories, and Marion Laboratories' diltiazem are calcium channel blockers.

Doctors are encouraged both by the effectiveness of ACE inhibitors and channel blockers in lowering blood pressure and by the avoidance of psychiatric and sexual disorders as side effects. The Joint National Committee on Detection, Evaluation & Treatment of High Blood Pressure has included both classes of drugs as first-step treatment of

hypertension [*Arch. Int. Med.*, 148, 1023 (1988)].

Enalapril is approved by the Food & Drug Administration to treat hypertension and severe cases of heart failure. Captopril is approved for hypertension and both mild and severe heart failure. Lisinopril is approved for hypertension only, but Merck probably will win approval for enalapril and lisinopril for all cases of heart failure soon.

Habermas sees explosive growth potential for ACE inhibitors for both hypertension and heart failure. He estimates 33% annual growth to $2 billion in 1992 from $471 million in 1987. Though several other companies will get approval for ACE inhibitors, Habermas says that most sales will come from captopril, enalapril, and lisinopril.

The Bernstein analyst also expects growth of 31% annually for calcium blockers to $2.8 billion in 1992 compared with $738 million in 1987. This growth will come not only from hypertension but also from cases of angina, heart failure, heart attack, arrhythmias, silent ischemia, stroke, and senility. Silent ischemia is atherosclerosis that has begun to affect the heart adversely but does not yet show symptoms.

Thus, combined sales of ACE inhibitors and calcium blockers could reach $5 billion in the mid-1990s, which will be half the sales of all cardiovascular drugs.

One source of calcium ions, which cause contraction of smooth muscle in arterial walls, is inflow through ion-specific channels. Drugs such as diltiazem and nifedipine block these channels, limiting inflow of calcium and keeping muscle cells in relaxed states for a longer time.

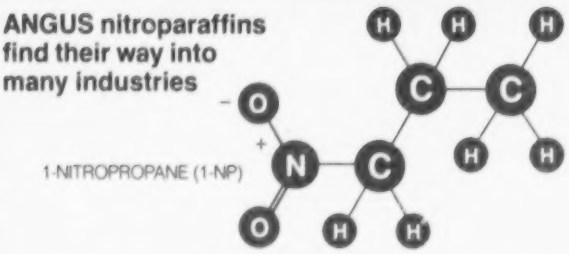
Death rates from heart disease stay high despite progress

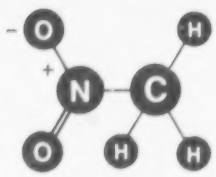
Cause	Deaths per 100,000 population				
	1985	1980	1975	1970	1965
Major cardiovascular diseases	409.6	436.4	450.7	496.0	504.5
Heart disease	323.0	336.0	332.4	362.0	367.4
Rheumatic fever & heart disease	2.8	3.5	6.0	7.3	8.0
Hypertensive heart disease	9.9	10.9	5.1	7.4	28.4
Ischemic heart disease	224.8	249.7	298.3	328.1	309.4
Other disease of endocardium	4.0	3.2	2.0	3.3	6.6
Other heart disease	81.5	68.7	20.9	15.9	15.1
Hypertension	3.2	3.5	2.9	4.1	6.0
Cerebrovascular disease	64.1	75.1	90.1	101.9	103.7
Atherosclerosis	10.0	13.0	13.4	15.6	19.7
Other	9.2	8.8	11.9	12.5	7.7

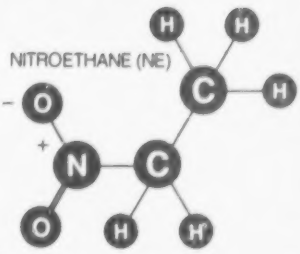
Source: National Center for Health Statistics

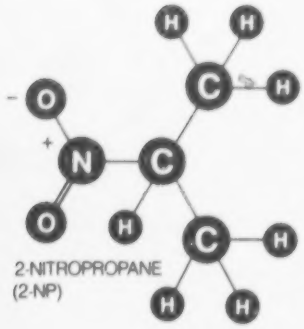
Nitroparaffin building blocks for synthesis chemists

ANGUS nitroparaffins find their way into many industries









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For now, FDA approval of most calcium blockers is limited to angina, although the verapamil of Knoll Pharmaceuticals and G. D. Searle & Co. is also approved for hypertension and arrhythmia. Angina is chest pain brought on by exercise, which increases heart rate and thus the heart's own need for oxygen. Narrowing of coronary arteries by atherosclerosis limits flow of oxygenated blood to the heart, starving the muscle and causing pain. Some patients also have vasospastic angina, in which coronary arteries constrict suddenly.

In addition to hypertension, high blood serum cholesterol is also a risk factor for atherosclerotic heart disease. Both the American Heart Association and National Institutes of Health recommend that cholesterol levels be reduced below 200 mg per deciliter. And the National Cholesterol Education Program Expert Panel has estimated that when concentrations are 250 to 300 mg per dL, each 1% reduction in cholesterol yields a 2% reduction in coronary heart disease rates [*Arch. Int. Med.*, **148**, 36 (1988)].

Two promising kinds of drugs to lower blood cholesterol levels are bile acid-binding resins and hydroxymethylglutarylcoenzyme A (HMG-CoA) reductase inhibitors.

Two bile acid-binding resins are Bristol Laboratories' cholestyramine and Upjohn's colestipol. Cholestyramine is a copolymer of styrene and trimethyl-*p*-vinylbenzylammonium chloride crosslinked with divinylbenzene. Colestipol is an insoluble polymer of indefinite structure made from diethylenetriamine and epichlorohydrin.

The only HMG-CoA reductase inhibitor approved by FDA to date is Merck's lovastatin. Merck also has developed simvastatin, which may be the company's entry to foreign markets, and Squibb is seeking U.S. approval for eptastatin.

Binding resins complex bile acids in the intestine for excretion in feces. Without such binding, bile acids would be reabsorbed from the intestine for reuse. Bile acids emulsify dietary fat for better digestion and are synthesized in the body from cholesterol. Enhancing excretion of bile acids shifts the equilibrium toward consumption of cholesterol.

One attraction of binding resins is that they are not absorbed in the body and so are not systemic agents. Drawbacks are that patients must consume 30 to 55 g per day, and they cause constipation in up to 20% of patients.

Physician David H. Blankenhorn led a team at the University of Southern California whose study showed that binding resins can play important roles in improving status of heart patients [*J. Am. Med. Assoc.*, **257**, 3233 (1987)]. They treated 81 men who had had coronary bypasses with a low-cholesterol diet, colestipol, and niacin, which is also a cholesterol-lowering agent. Another 81 such men got dietary treatment only.

After two years, x-rays of grafts and natural coronary arteries showed regression of atherosclerotic plaques in 16.2% of the drug group and 2.4% of the diet-only group. In the drug group, 61% had stable or improved

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heart status versus 39% of the diet group. Serum cholesterol fell 26% in the drug group versus 4% in the diet group.

HMG-CoA reductase inhibitors block the enzyme that catalyzes conversion of β-hydroxy-β-methylglutarylcoenzyme A to mevalonic acid on the pathway to synthesis of cholesterol from acetylcoenzyme A. Rendered incapable of making cholesterol for themselves, liver cells respond by increasing the number of low-density lipoprotein (LDL) receptors on their surfaces.

LDL is the serum cholesterol-transporting substance that is prone to deposit cholesterol on artery walls. LDL receptors enable liver cells to absorb LDL for degradation, thus freeing cholesterol for use inside cells. This absorption also lowers serum concentrations of LDL-cholesterol. High-density lipoprotein (HDL) levels are unaffected and sometimes even raised. High HDL levels have been correlated with low incidence of heart disease and may be protective. Though the resulting reduction in serum cholesterol should be beneficial, no studies have been completed to show that HMG-CoA reductase inhibitors prevent or reverse atherosclerosis.

Habermas projects yearly sales increases of 39% for cholesterol-lowering agents to $1 billion in 1992 from $200 million in 1987. Though other oral agents are approved for cholesterol lowering, the lower incidence of side effects will garner almost 70% of prescriptions for the HMG-CoA reductase inhibitors, eptastatin, lovastatin, and possibly symvastatin, he says.

In addition to cholesterol deposition, blood platelet aggregation is a component of atherosclerosis. This may result from disruption of the balance between aggregation stimulators produced by platelets and aggregation inhibitors secreted by cells of arterial inner walls.

Newer understanding of this balance has led doctors to prescribe aspirin for angina, following a heart attack, and even as a preventive measure for middle-aged persons with no signs of heart disease. Aspirin is an inhibitor of cyclooxygenase, which catalyzes conversion of arachidonic acid released from fats to prostaglandin H_2 (PGH_2).

PGH_2 is the precursor of both thromboxane A_2 (TXA_2), which promotes aggregation and constricts arterial smooth muscle, and prostacyclin, which inhibits aggregation. Platelets are highly specialized cells that are incapable of protein synthesis. Thus, once a cell's cyclooxygenase is inhibited, it cannot make more. One aspirin tablet daily is enough to suppress TXA_2 production in the whole population of platelets as the body forms new platelets to replace those that are scavenged.

Once under way, atherosclerotic heart disease may appear as angina or heart attack. Heart attack usually

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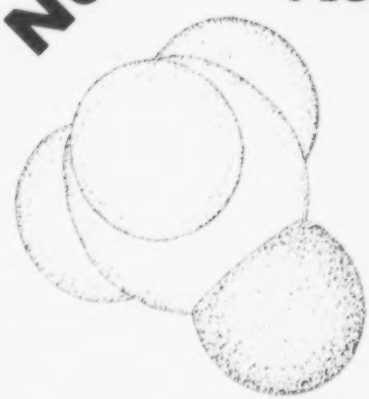

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What cardiac drugs are

Atherosclerosis in the heart is occlusion of the coronary arteries, by combined proliferation of smooth muscle cells, aggregation of blood platelet cells, and deposition of cholesterol.

Atherosclerotic heart disease results in angina (chest pain on exertion), ischemia (partial deprivation of oxygenated blood), and myocardial infarction (heart attack). Accumulated damage to heart muscle by ischemia and heart attacks can lead to arrythmias (abnormal heart rhythms) and heart failure.

But hypertension (high blood pressure) and hypercholesterolemia (high blood cholesterol) are among conditions that accelerate atherosclerosis. And hypertension is also a cause of heart failure independent of atherosclerosis.

Some of the same drug types that control hypertension are also effective against angina and heart failure. And decisions about which antihypertensive drugs to prescribe must be weighed against their effects on arrhythmias, blood cholesterol, and heart failure.

Thus in a sense, hypertension, hypercholesterolemia, angina, heart attack, arrhythmias, and heart failure are all bound up in atherosclerotic heart disease, and the drugs used to treat these conditions are broadly cardiac drugs. Newer examples of these are α-adrenergic blockers (hypertension), β-adrenergic blockers (hypertension and angina), diuretics (hypertension and heart failure), calcium channel blockers and angiotensin-converting enzyme inhibitors (hypertension, angina, heart failure, and heart attack), vasodilators (angina and heart failure), inotropes (heart failure), and hydroxymethylglutarylcoenzyme A reductase inhibitors (cholesterol lowering).

results from lodging of a blood clot in a narrowed coronary artery. This acute shutting off of oxygenated blood causes death of some heart muscle. Some heart attacks come from a spasm of a coronary artery that is free of atherosclerosis. Accumulating damage from ischemia, heart attacks, and untreated hypertension produces heart failure. Heart failure is a gradually declining ability of the heart to pump sufficient blood.

Angina occurs owing to insufficiency of coronary arteries to meet oxygen demands of heart muscle. Attacks are brought on by exercise or anxiety, which increase the work of the heart and thus its oxygen demand. Symptoms include a crushing sensation in the chest, abdominal pain, and/or pain radiating from the chest to the left arm, throat and jaw, and sometimes to the right arm.

Treatment of an attack centers around easing the work of the heart

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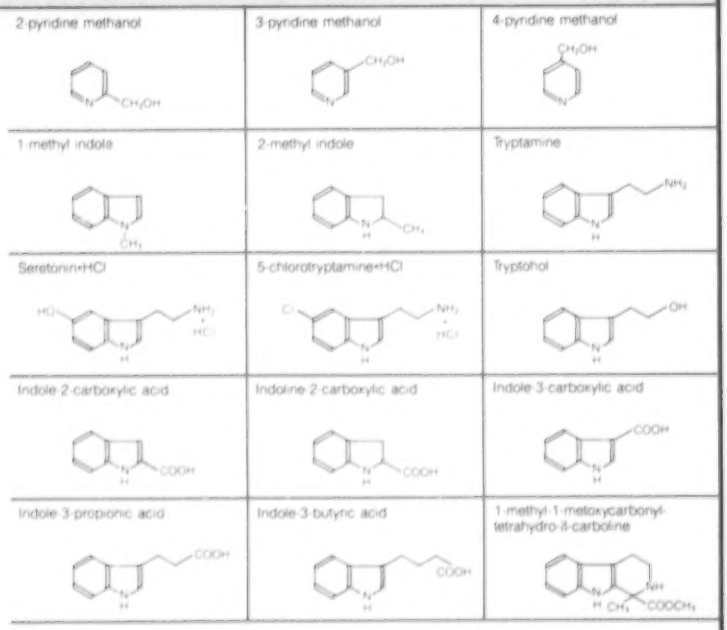

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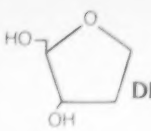
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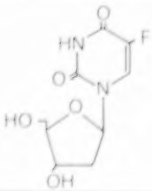
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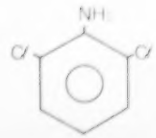
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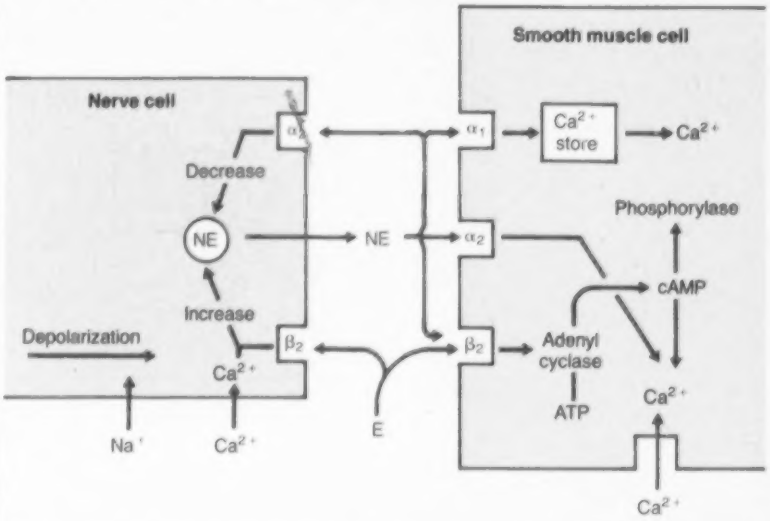
Nerve signal triggers mechanism of muscle contraction



Wave of electrical depolarization cascades down nerve toward synapse as sodium ions rush into succeeding segments. At the synapse, depolarization draws calcium ions into the nerve cell also. Calcium causes storage vesicles to expel norepinephrine (NE), which flows into the synapse. Norepinephrine activates α_1-, α_2-, and β_2-receptors of smooth muscle cell; activation of α_2-receptors of nerve cell suppresses further norepinephrine release as a control mechanism. Epinephrine (E), secreted into bloodstream as a result of stress, also activates β_2-receptors. Activation of α_1-receptors causes release of free calcium ions from smooth muscle cell stores. Activation of α_2-receptors stimulates entry of calcium ions into smooth muscle cell. Activation of β_2-receptors triggers adenyl cyclase to convert adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). cAMP also stimulates entry of calcium ions and activates phosphorylase. Calcium ions alter crosslinking of proteins actin and myosin, producing muscle contraction. Phosphorylase mobilizes glycogen to provide energy for muscle contraction.

and thus its oxygen demand. Long-term treatment of angina includes loss of excess weight, stopping smoking, exercise, and treatment of hypertension and high blood cholesterol if present.

Drugs used to treat angina are nitrate ester vasodilators, β-adrenergic blocking agents, and calcium channel blockers. One such nitrate is nitroglycerine, available as tablets placed under the tongue and ointments and impregnated adhesive patches for absorption through the skin. Nitroglycerine tablets are effective in minutes and last a half hour. Longer-acting oral nitrates include isosorbide dinitrate and pentaerythritol tetranitrate. Nitrates dilate veins, thus reducing blood pressure against which the heart must work.

β-Blockers check stimulation of the heart by the sympathetic nervous system, thus reducing heart rate. Calcium blockers are vasodilators that reduce blood pressure and inhibit spasms of coronary arteries.

About 1.5 million Americans suffer heart attacks annually, of which 750,000 are fatal. The key diagnostic tool is the electrocardiogram (EKG), which shows characteristically abnormal patterns.

Laboratory tests indicate heart muscle death by results such as increased red blood cell sedimentation rates, increased white cell counts, and raised serum levels of creatine kinase. Creatine kinase occurs as three isozymes called MM (in skeletal muscle), BB (in the brain), and MB (in the heart). Sensitive immunoassays can detect the

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In the past, doctors could treat heart attacks only by decreasing the heart muscle's oxygen needs to limit the amount of muscle death and by waiting for the blood clot in the coronary artery to dissolve naturally. Intravenous morphine relieves pain and anxiety; lidocaine corrects arrhythmias; atropine increases an abnormally slow heartbeat; β-blockers lower heart rate to reduce muscle work; and nitroglycerine, isosorbide dinitrate, or sodium nitroprusside lowers high blood pressure.

Plasmin helps dissolve the blood clot naturally by catalyzing chain breaking in the blood clotting protein fibrin. Plasmin is generated from the circulating precursor plasminogen by kinases.

In recent years, drug companies have developed such kinases as urokinase, streptokinase, and tissue plasminogen activator (t-PA) to treat heart attack. Until now, it was thought that these agents were effective only when delivered by a catheter directly into the coronary artery.

A catheter is a tube inserted by opening a distant artery and moving it through the arterial system via the aorta to the coronary artery. This arduous procedure requires specialized facilities available in only one out of five U.S. hospitals and must be done within six hours of onset of symptoms.

Most recent studies show that slow intravenous infusion of these kinases is also effective. And mortality rates drop even further when doctors give aspirin also to prevent reformation of blood clots.

Hoechst-Roussel Pharmaceuticals and KabiVitrum market streptokinase in the U.S., produced from cultures of hemolytic streptococci. Though streptokinase opens 60% of coronary arteries and has shown lower mortality rates, this bacterial protein causes allergic reactions in 10 to 15% of patients.

Beecham Laboratories has developed a complex of plasminogen with streptokinase whose active site is anisoylated. This agent has the advantage that it can be given as a single injection. Slow hydrolysis of

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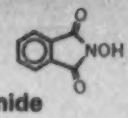

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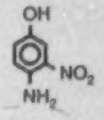
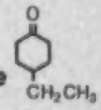
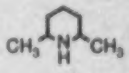


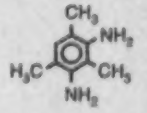
4-Amino-3-nitrophenol



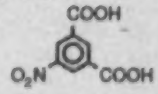
4-Ethylcyclohexanone



2,6-Dimethylpiperidine, cis



2,4-Diamino-1,3,5-trimethylbenzene (2,4-Diamino-mesitylene)



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the anisoyl group frees the active site of streptokinase for activation of the associated plasminogen. Beecham plans to apply for U.S. approval soon and has signed an agreement with Upjohn to market the drug in a combined effort.

Abbott Laboratories markets urokinase, made from tissue cultures of kidney cells, approved for treatment of heart attack by catheterization. The company is seeking additional approval for intravenous use of urokinase.

The only t-PA now approved in this country is that of Genentech, produced from cultures of Chinese hamster ovary cells and approved for intravenous use. The company used a plasmid to insert the human t-PA gene.

Genetics Institute is cooperating with Burroughs Wellcome Co. in clinical trials of t-PA. The two have formed WelGen Manufacturing Co. as a joint venture with a plant in Greenwich, R.I., to make t-PA and other agents derived from biotechnology.

Integrated Genetics has developed a modified t-PA in which the asparagine at position 120 is changed to glutamine. The change prevents glycosylation at that site and increases the half-life to 30 minutes from two to five minutes. For now, the company is testing only in Japan, with the firm Toyoba.

As a biotechnological alternative to aspirin to prevent reocclusion of coronary arteries, Centocor has produced monoclonal antibodies against the blood platelet glycoprotein IIb/IIIa receptor. Centocor also expects the product to be effective against reocclusion following coronary angioplasty.

Coronary angioplasty is a procedure to treat angina by inserting a balloon through a catheter into the coronary artery. On positioning the balloon at the narrowed site, doctors inflate the balloon, which compresses the atherosclerotic plaque and widens the artery.

Controversy has erupted over the relative costs of clot-dissolving kinases. The amount of streptokinase for a course of treatment costs about $200, whereas that of Genentech's t-PA is $2200. Abbott spokesmen say that the cost of urokinase also

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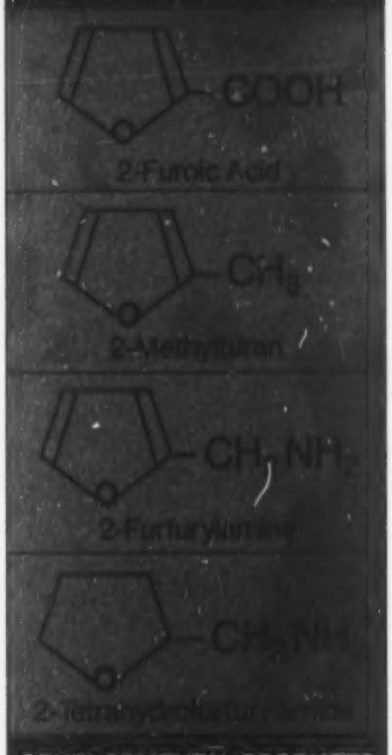

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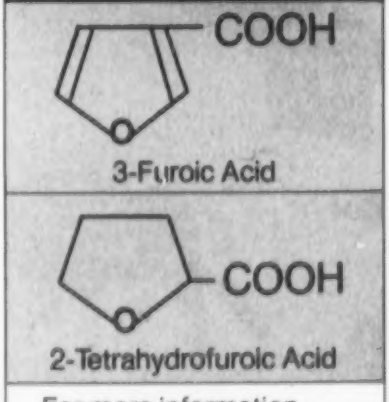

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would be about $2200. Beecham has not set a U.S. price for its anisoylated plasminogen-streptokinase activator complex (APSAC), but it probably will be much higher than that for streptokinase.

The U.S. Prospective Payment Assessment Commission, which makes recommendations about what procedures Medicare and Medicaid should pay for, has decided that there are no clinical differences between streptokinase and t-PA, and that the higher cost of t-PA is not justified. This picture could change with the publication of results of studies of whether or not t-PA lowers mortality rates.

Genentech has offered to reimburse hospitals for the cost of its t-PA used to treat indigent patients. Such patients must earn less than $25,000 per year and not be covered by private or government health insurance.

Dissolving of a clot in a coronary artery leads to sudden reperfusion of heart muscle with oxygenated blood. Sudden reperfusion can lead to tissue damage. Biochemistry professor Joe M. McCord of the University of South Alabama and his collaborators have suggested that this damage is caused by oxygen-derived free radicals. The enzyme superoxide dismutase (SOD) prevents formation of such radicals and thus may play a role in treatment of heart attack.

In this view, oxygen starvation in heart muscle leads to metabolism of adenosine triphosphate to hypoxanthine. Ordinarily, hypoxanthine would be converted to xanthine harmlessly by xanthine dehydrogenase. But increased amounts of calcium entering heart muscle cells triggers change of the dehydrogenase to an oxidase.

Xanthine oxidase uses oxygen to produce xanthine and superoxide radical anion. Superoxide liberates iron from the protein ferritin, and the iron catalyzes formation of tissue-damaging hydroxyl radicals from superoxide.

Additionally, McCord has suggested that superoxide activates a blood factor that attracts cells called neutrophils to the site as part of an inflammation reaction. Neutrophils also produce superoxide. Thus, re-

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perfusion would lead to a burst of superoxide radicals within heart tissue, which would attract neutrophils to produce even more superoxide.

Therapy against reperfusion damage might include an anti-inflammatory drug to limit the process in the long term as well as SOD to limit the process throughout.

Firms involved in developing SOD include Bio-Technology General, Chiron, and Sterling Drug. Bio-Technology General is collaborating with Bristol-Myers to test SOD after angioplasty at Johns Hopkins University. Chiron's testing is limited to reperfusion damage to kidneys before transplant. Sterling has inherited the SOD program of Eastman Pharmaceuticals following acquisition of Sterling by Eastman Kodak.

Patients whose hearts are damaged by heart attack, ischemia, or untreated hypertension often develop heart failure. Heart failure is a progressive process in which the heart no longer pumps enough blood for the body's needs. About 2 million Americans suffer from the condition.

With atherosclerotic disease or hypertension, the process usually begins with enlargement of the left ventricle. The left ventricle is the chamber that receives oxygenated blood from the contracting left atrium and itself contracts to pump blood to the body through the aorta.

The left ventricle wall becomes increasingly stretched in the relaxed state and cannot contract with sufficient force to pump the normal fraction of blood it contains. This results in high filling pressures on the next delivery of blood from the atrium.

Receptors in the body detect the reduced output from the heart and respond by raising blood pressure. Increased blood pressure increases the work of the heart and causes further enlargement and reduced pumping capacity.

High filling pressures back up into the pulmonary system, causing high blood pressures there. High pulmonary vessel pressures force water through vessel walls to fill air sacs in the lungs. Blood flowing past fluid-filled sacs is not aerated,

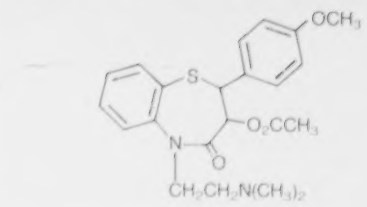
and this further reduces the quality of heart output.

Treatment of heart failure includes rest. The minor tranquilizer diazepam helps achieve this during the day and the hypnotic flurazepam at bedtime.

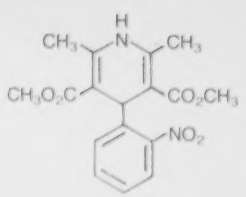
Associated high blood pressure is treated as hypertension with salt restriction, diuretics, and vasodilators. Just after diagnosis, doctors often use the potent, fast-acting, potassium-sparing diuretic furosemide. Digitalis suppresses arrhythmias that may develop in the weakened muscle, lowers heart rate, and increases contractile force.

But until recently, despite drug treatment that relieved symptoms and increased ability to exercise without fatigue and breathing difficulties, mortality rates were 50% within five years of diagnosis. Then, long-term studies by the Veterans Administration [*New England J. Med.*, **314**, 1547 (1986)] showed an average 28% improvement in survival rates using hydralazine and isosorbide nitrate. Hydralazine is an arterial dilator and isosorbide dinitrate a venous dilator. In the Cooperative North Scandinavian Enalapril Survival Study, a consortium of doctors showed similar improvements of survival rates with the ACE inhibitor enalapril [*New England J. Med.*, **316**, 1429 (1987)]. These results offer hope that medicinal chemists can discover new agents that actually improve survival rates in heart failure. □

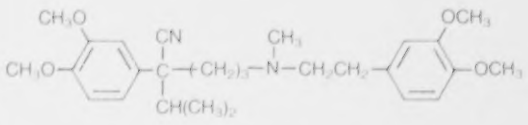
Sales of calcium channel blockers to hit $2.8 billion in '92



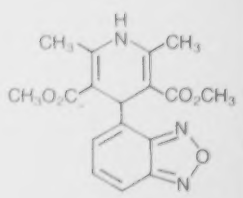
Diltiazem



Nifedipine



Verapamil



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